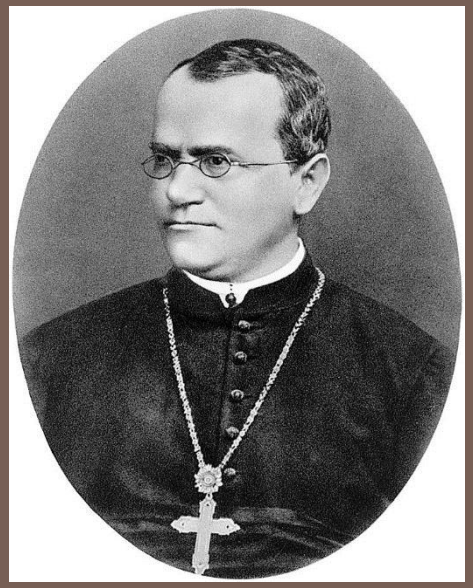


By Iltis, Hugo - [1], CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=33070385

By Uwe Dettmar/Paul-Ehrlich-Stiftung - Public Domain, https://commons.wikimedia.org/w/index.php?curid=37848244

WE'RE WAY PAST PEAS:
USES OF GENETIC INFORMATION TO UNDERSTAND HUMAN HEALTH AND GUIDE HEALTH CARE DECISION MAKING

Diana Nelson Louden, UW Health Sciences Library
Carolyn Martin, NN/LM Pacific Northwest Region

Topics for Today

- Basic principles of genetics
- Uses of genetics in health care; genetic testing

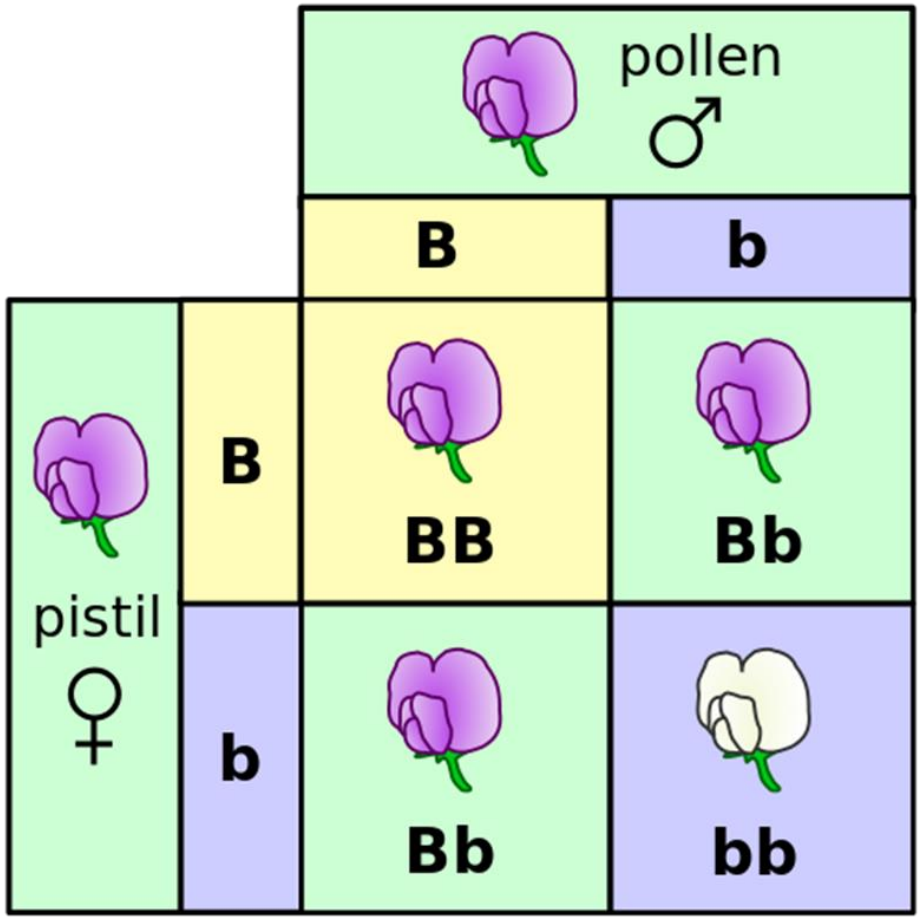
- BREAK

- NCBI MedGen portal; other clinical genetics resources.
- Answer practice questions using MedGen
- Genetic health literacy & genetic science literacy
- Genetic consumer health resources
- Direct-to-consumer testing
- Ethics and privacy
- Precision Medicine Initiative

Presentation slides are available at: https://nnlm/gov/pnr/training/presentations

Mendel Discovered Patterns of Inheritance by Studying Physical Traits

Before genes were discovered, Mendel realized that he could make mathematical predictions about the inheritance of physical traits – like flower color.



By Madprime (Own work) [CC0, GFDL (http://www.gnu.org/copyleft/fdl.html), CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0/) , via Wikimedia Commons

Mary-Claire King: Way Past Peas!

Mary-Claire King: Way Past Peas!

Transforming the Diagnosis and Prevention of Breast Cancer

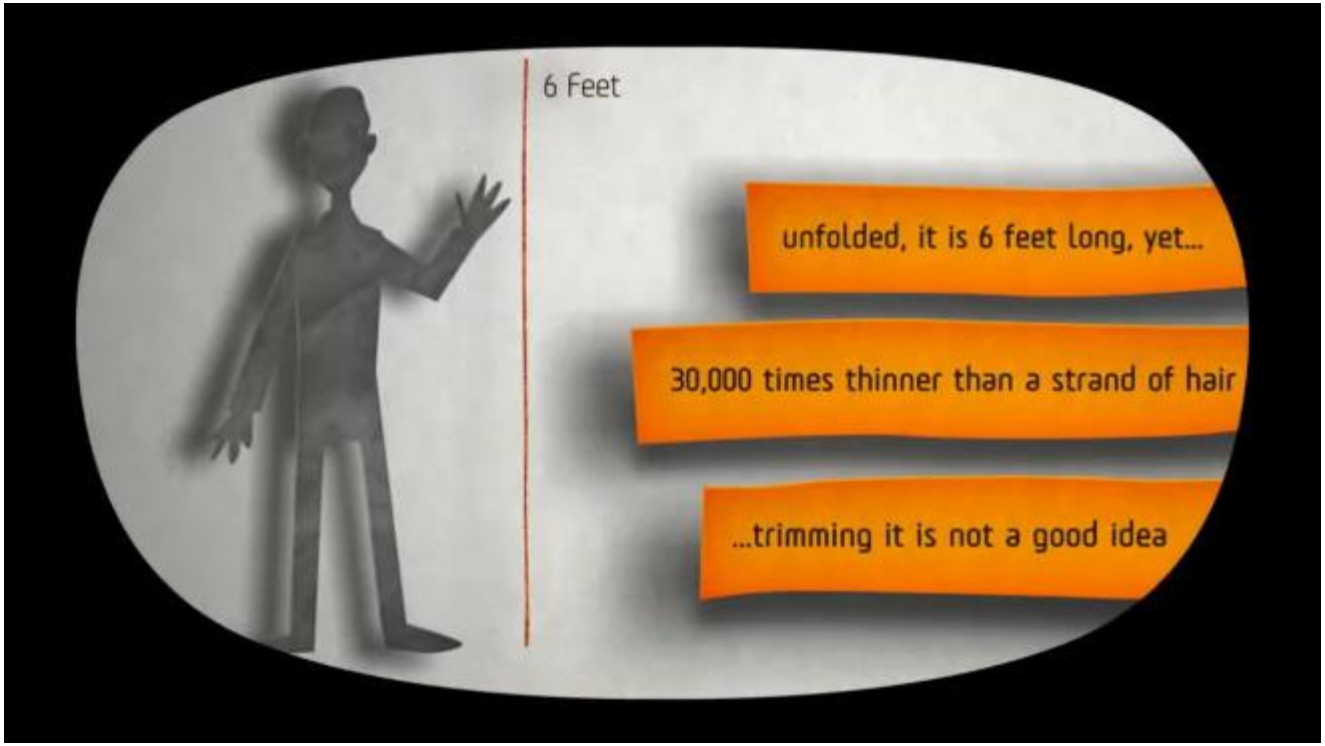
- Some cases of breast cancer clustered in families; must be inherited.
- In 1990 demonstrated that a single gene, which she named BRCA1, was responsible for breast and ovarian cancer in many families.
- Studied how mutations in BRCA1 lead to breast cancer. (BRCA1 is a tumor suppressor gene.)
- Now recommends that all women should be offered genetic testing for BRCA1 and BRCA2 mutations at about age 30 as part of routine medical care. "About half of women who inherit mutations in BRCA1 or BRCA2 have no family history of breast or ovarian cancer and have no idea they are carrying cancer-causing mutations."
- "Most of inherited breast and ovarian cancer can be prevented, if mutation carriers know who they are."

http://www.nytimes.com/2015/02/10/science/mary-claire-kings-pioneering-gene-work-from-breast-cancer-to-human-rights.html

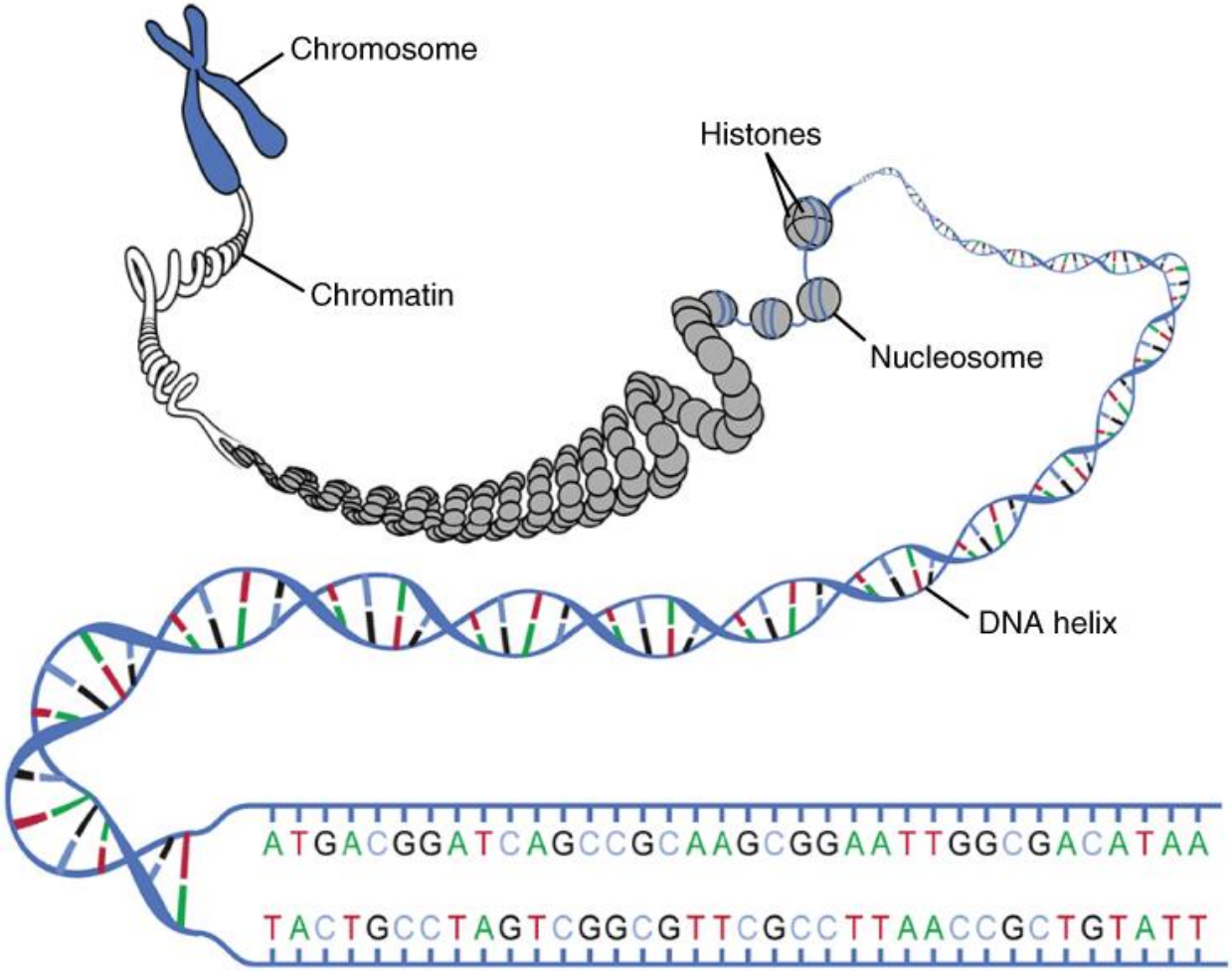
The Animated Genome

Unlocking Life's Code video

https://unlockinglifescode.org/media/animations/659#660

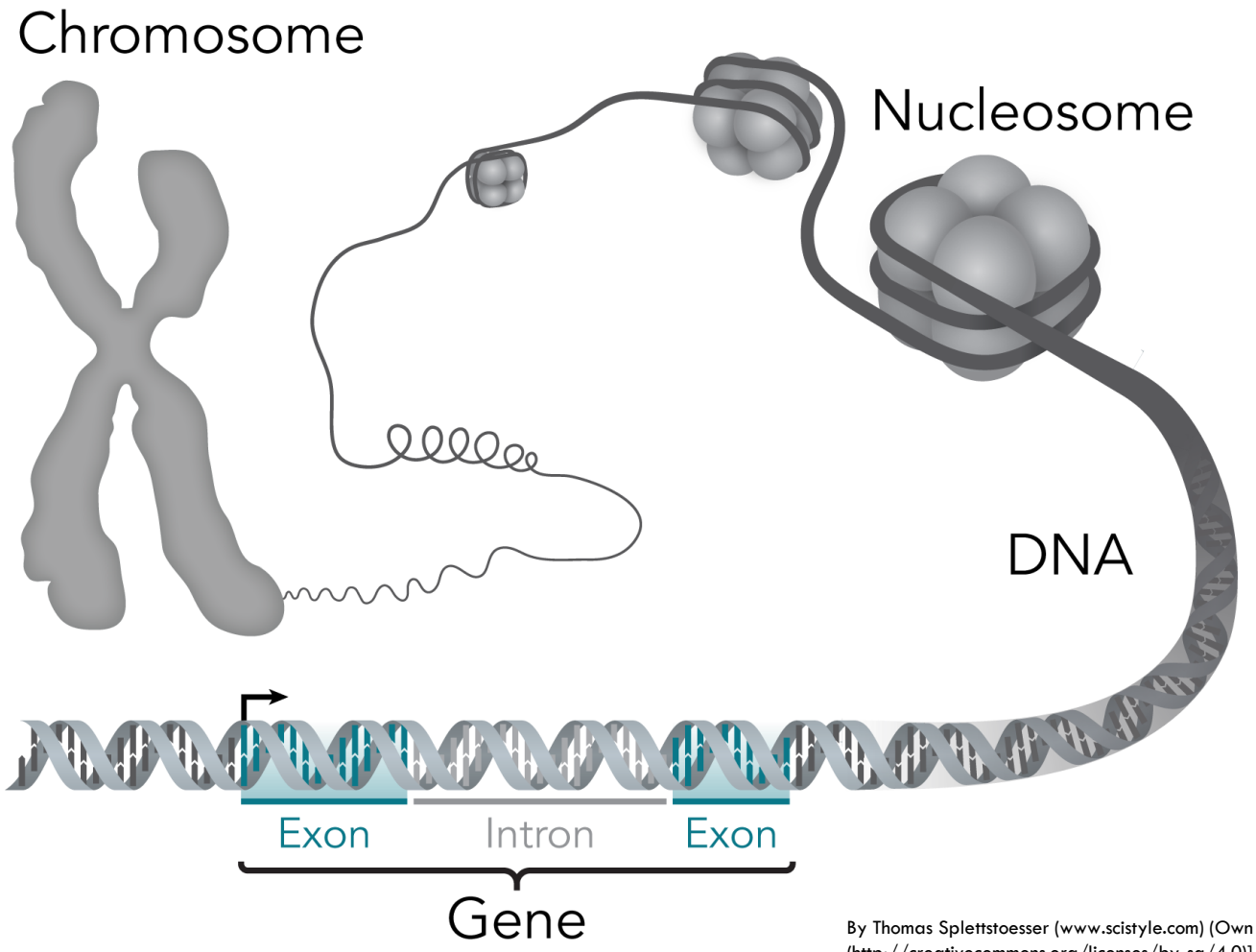


Chromosomes are made of DNA



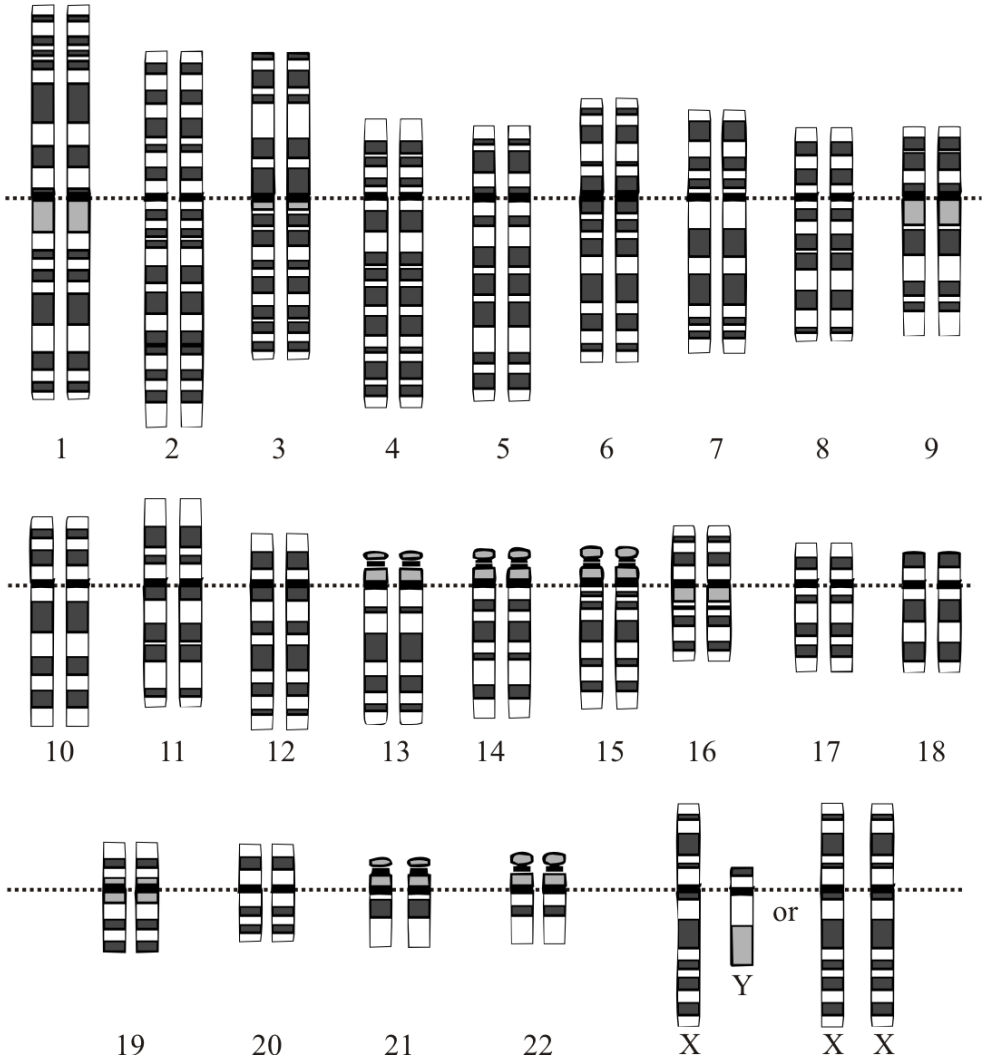
By OpenStax College [CC BY 3.0 (http://creativecommons.org/licenses/by/3.0)], via Wikimedia Commons

Genes are discrete segments of DNA found on chromosomes



By Thomas Splettstoesser (www.scistyle.com) (Own work) [CC BY-SA 4.0 (http://creativecommons.org/licenses/by-sa/4.0)], via Wikimedia Commons

Humans Receive 23 Chromosomes from Each Parent; Each of Your Cells Contains These 46 Chromosomes*

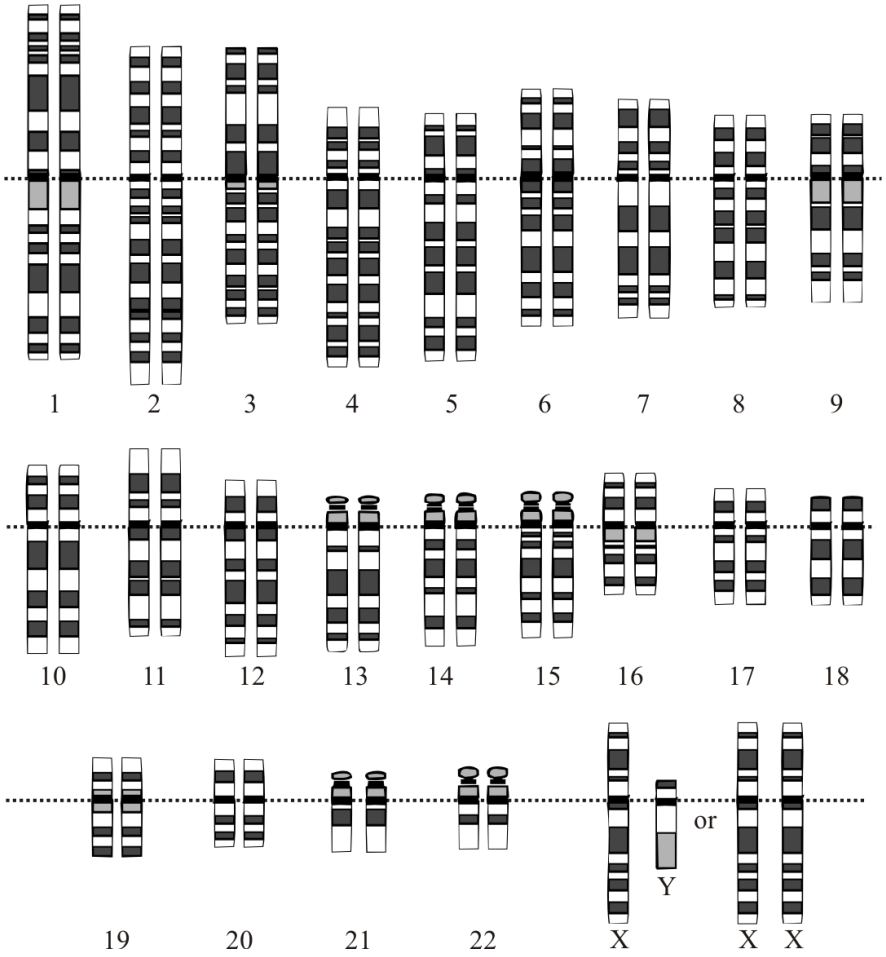


*Egg and sperm cells only contain one set of 23 chromosomes.

By Courtesy: National Human Genome Research Institute [Public domain], via Wikimedia Commons

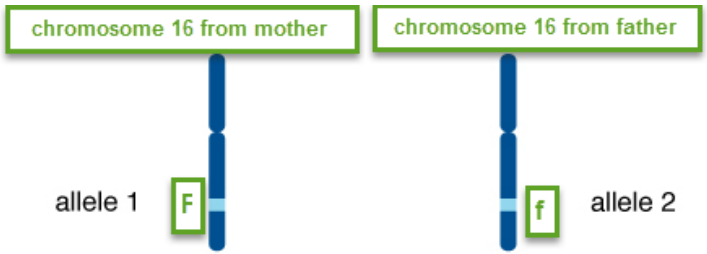
This is Your Genome

- The DNA that contains your 20,000+ genes.
- The DNA that regulates the expression of your genes.
- The DNA of unknown significance.

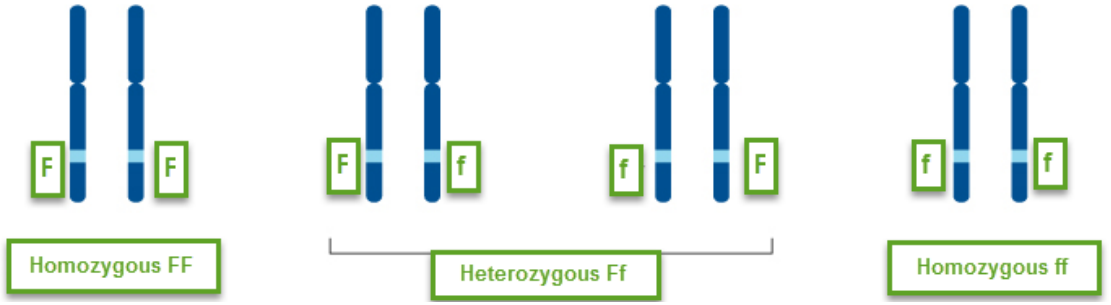


Each pair of chromosome has the same genes at the same locations, but possibly different alleles (versions).

"F" represents the freckle gene – MC1R on chromosome 16. Freckles are a dominant trait, so if you receive at least one copy of the F allele, you are likely to have freckles.



An allele is one of two or more versions/variants of a gene within a population.



Many Traits Are Multigenic – the Product of Multiple Genes

Eye color is determined by variation at several different genes and the interactions between them.

Brown Eyes

How does a gene affect a physical trait or process?

- Genes encode proteins.
- The DNA sequence dictates the amino acid sequence of the protein.
- Proteins do the work in your body.

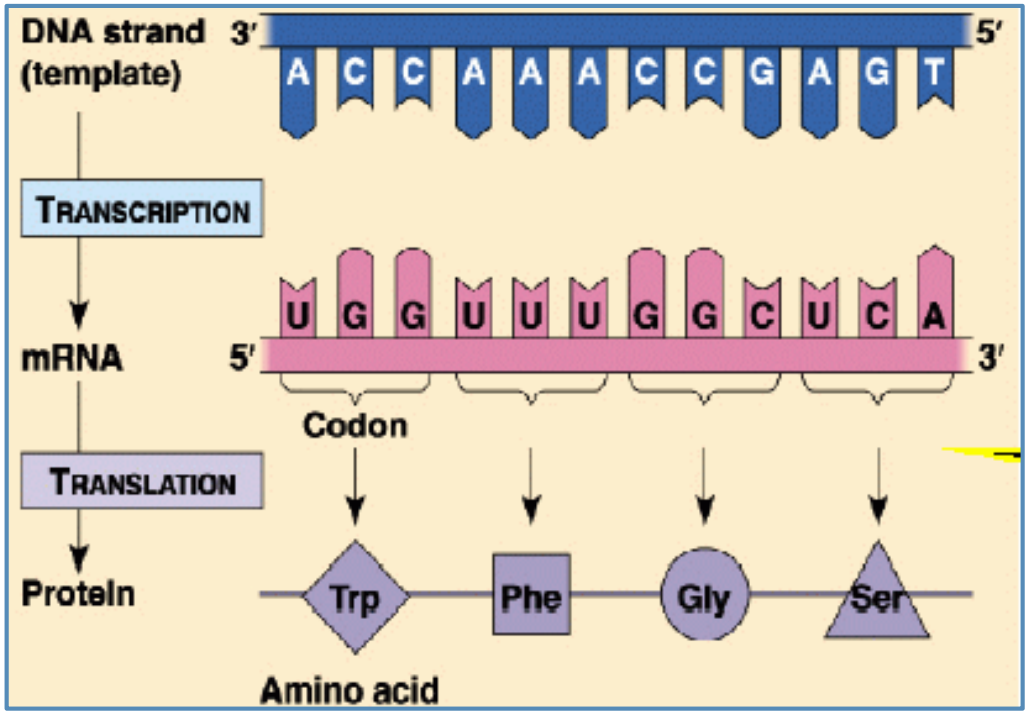
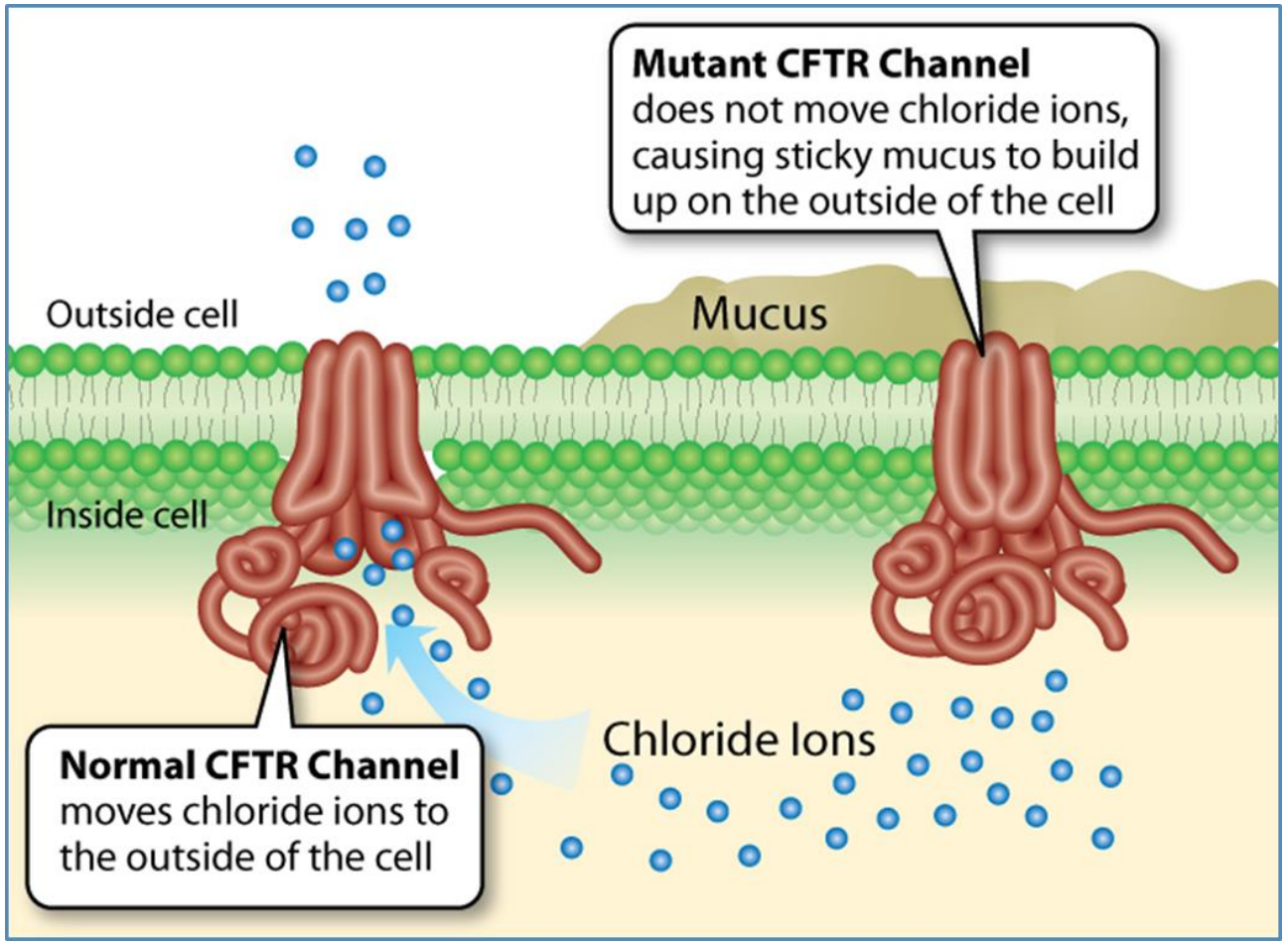


Image credit from Harvey Mudd College web page:
http://fourier.eng.hmc.edu/bioinformatics/intro/node8.html

NOT ALWAYS!

Altered genes can lead to altered proteins which can lead to disruptions in normal processes

NOT ALWAYS!



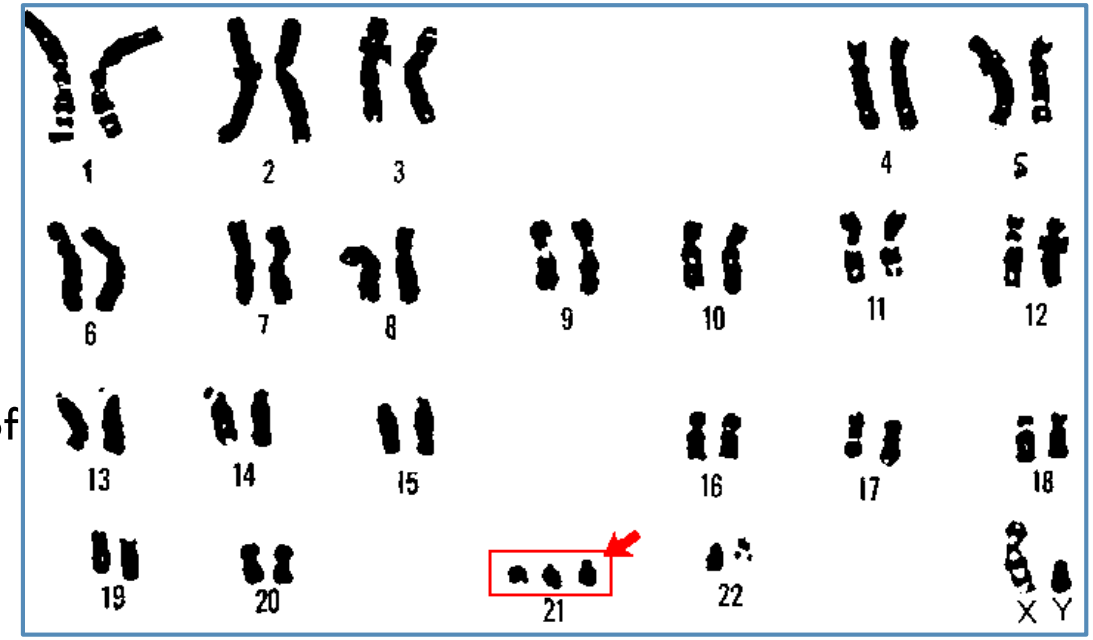
Genetic Science Learning Center, University of Utah,
http://learn.genetics.utah.edu

CATEGORIES OF DISEASES ATTRIBUTED TO GENES

- Chromosomal Diseases
- Monogenic Diseases
- Multifactorial Diseases

Chromosomal Diseases (Chromosomal Alterations)

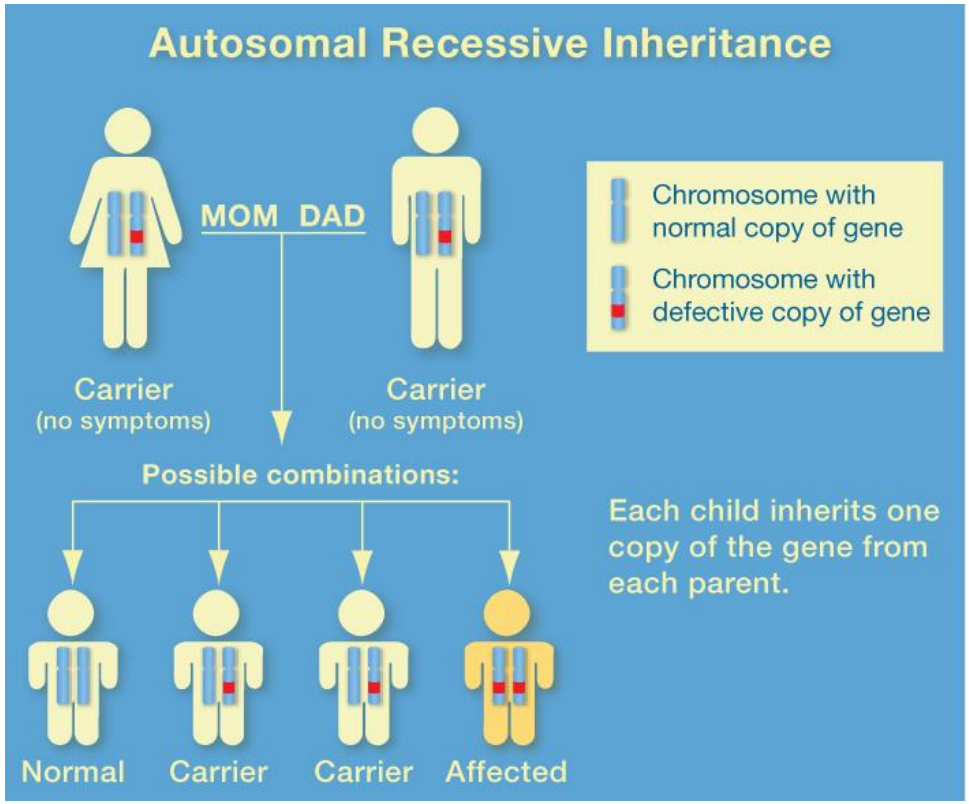
- An individual may have a missing chromosome, extra copies of a chromosome, or a portion of a chromosome may be deleted, duplicated, or translocated.
- Alteration may be inherited or *de novo*. Most originate in the egg or sperm.
- Examples: **Down's syndrome** (extra copy of chromosome 21) or **Prader-Willi syndrome** (microdeletion from short arm of chromosome 15)



By U.S. Department of Energy Human Genome Program. [Public domain], via Wikimedia Commons

Monogenic Diseases/ Mendelian Diseases

- Single-gene diseases follow the patterns of inheritance that Mendel discovered in his studies of pea plants.
- These rare inherited diseases tend to be caused by mutations in a single gene.
- Examples: cystic fibrosis, sickle-cell anemia, muscular dystrophy, and Huntington's disease.



Genetic Science Learning Center, University of Utah, http://learn.genetics.utah.edu

Multifactorial Diseases

- Complex diseases are caused by variation in many genes. They may also be influenced by environmental factors.
- The vast majority of human diseases fall into this category.
- Identifying the genes that contribute to these diseases has been difficult.
- Examples: cardiovascular disease, cancer, diabetes, and a number of birth defects and psychiatric disorders.

Credit: Nature's Scitable website -
http://www.nature.com/scitable/topic/genes-and-disease-17

Multifactorial Disease!

Type 2 Diabetes: A Multifactorial Disease

According to a 2016 review article by Kaul and Ali

- "Type 2 diabetes (T2D) is a multifactorial anomaly involving **57 genes** located on 16 different chromosomes and **136 single nucleotide polymorphisms (SNPs)**."
- "Genetic components have their own **pathways** encompassing insulin secretion, resistance, signaling, and β-cell dysfunction."
- "**Environmental factors** include epigenetic changes, nutrition, intrauterine surroundings, and obesity."
- "In addition, **ethnicity** plays a role in conferring susceptibility to T2D."

Kaul N, Ali S. Genes, Genetics, and Environment in Type 2 Diabetes: Implication in Personalized Medicine. DNA Cell Biol. 2016 Jan;35(1):1-12. PubMed PMID: 26495765

What Can I Blame My Parents For?

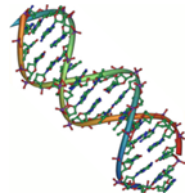
Heritability Estimates for Complex Traits

Bone Mineral Density	**50-85%**
Osteoarthritis	50%
Coronary artery disease	40-60%
Breast Cancer	25-45%
Neuroticism	6-15%
Ulcerative colitis	4-15%

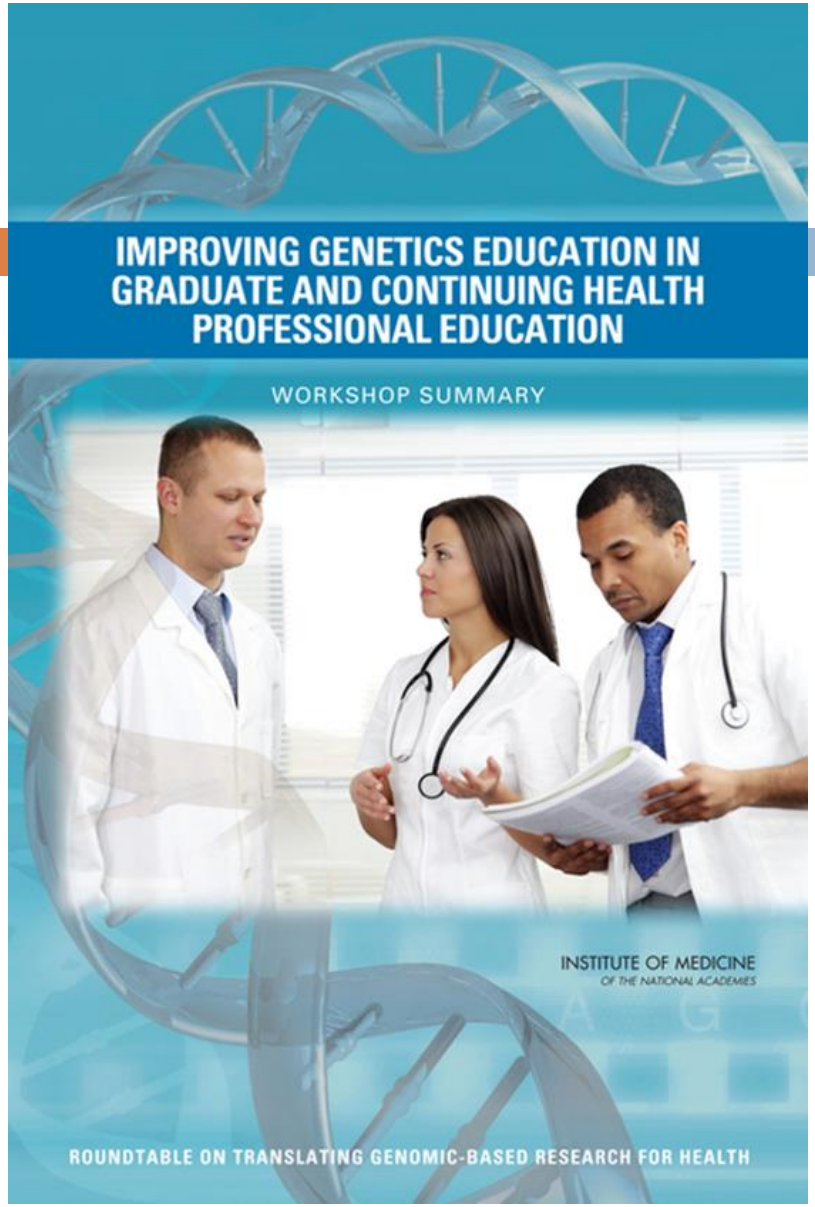
Heritability estimate – genetics accounts for what % of a person's susceptibility to a condition. Complex traits also due to other biological and environmental factors.

Numbers gathered from various recent articles.

How Are Changes in Genetics Affecting Health Care?



- Researchers learn more about genes and variants and disease risk every day.
- Capabilities for precision medicine are increasing.
- Health care providers ***other*** than medical geneticists and genetic counselors are dealing with genetic information.
- Clinicians may not have had much (recent) training in genetics.
- Genetic testing is a subject that patients may raise.
- Translating research findings to the clinic – do any of them apply to my patients?



"Despite the growing use of genomic applications in clinical practice, health professional knowledge about genomic information and confidence in using it have not kept pace….

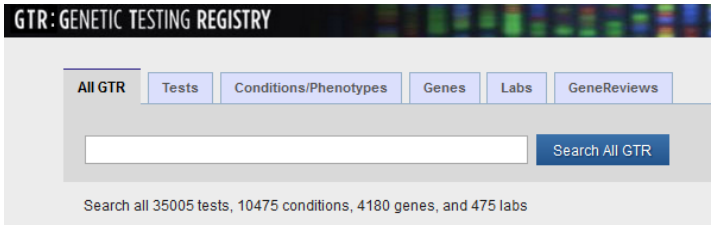
Many health care providers do not have either the knowledge or the tools they need in order to apply genetic information in their day-to-day practices.

This lack of support is contributing to a substantial delay in the translation of genetic research findings, when appropriate, into improvement in patient outcomes within the health care system."

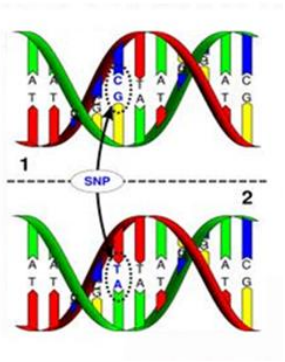
– Institute of Medicine 2015 report

Four Areas Where Genetics Is Intersecting Health Care

Diagnostic Testing



Single Nucleotide Polymorphisms



Graphic by Diane Rein – modified from Science Magazine, December 21, 2007

Tumor Genomic Testing

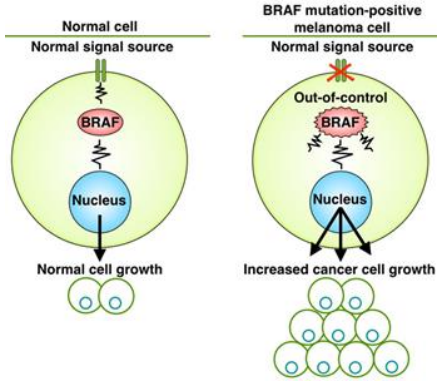
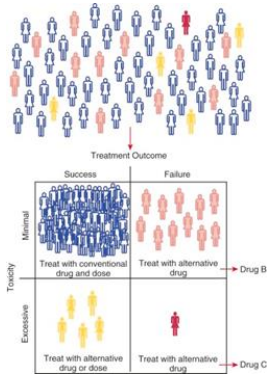


Image credit Incyte Pathology blog:

https://incytepathology.wordpress.com/2012/04/10/braf/

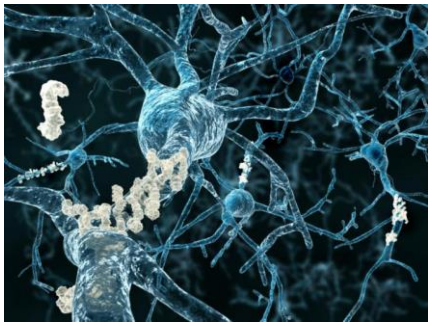
Pharmacogenomics



(Adapted from Yaffe SJ, Aranda JV: *Neonatal and pediatric pharmacology* , ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)

1. Diagnostic Testing – Does He Have Alzheimer's Disease?

Clinicians Don't Test Everyone.



Practice guidelines recommend testing for 3 genes associated with early onset AD in these 3 populations:

1) symptomatic patients with early onset AD;
2) individuals with a family history of dementia with one or more cases of early onset AD;
3) individuals with a relative affected by a known mutation of *APP*, *PSEN1*, or *PSEN2*.

Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. 2011. PMID:21577118

Beta-amyloid plaques picture: https://www.flickr.com/photos/35049835@N00/16867428955

The Answer to a Genetic Test Is Often Something Other Than Yes or No.

Labs Typically Report an Individual's Genetic Test Results Using Five Categories

1. Disease-causing mutation found.
2. Mutation found is **likely** disease-causing.
3. Mutation found is **probably** benign and not disease causing.
4. Mutation is known to be benign and does not cause disease.
5. Mutation is a "Variant of **Unknown** Significance" (VUS).

Genetic Test Results Require Interpretation

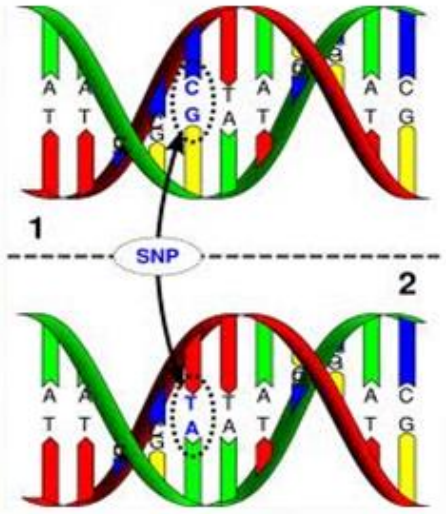
- Clinicians don't order genetic tests unless the results are likely to improve patient management.
- Typically Medical Geneticists and Genetic Counselors are the clinicians who are most qualified to order and interpret genetic tests.

Genetic Test Registry
http://www.ncbi.nlm.nih.gov/gtr/

Polymorphism in Nature

By Debivort - Own work by Author, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1626674

2. Genetic Variants – Single Nucleotide Polymorphisms



Single Nucleotide Polymorphisms (SNPs)

	SNP	SNP
Individual 1	AACACGCCA....	TTCGGGGTC....
Individual 2	AACACGCCA....	TTCGAGGTC....
Individual 3	AACATGCCA....	TTCGGGGTC....
Individual 4	AACACGCCA....	TTCGGGGTC....

Graphic by Diane Rein – modified from Science Magazine, December 21, 2007.

Over 1,600 SNPs Have Been Identified in the BRCA1 Gene.

Here is one of those SNPs.

Rs55770810

rs55770810, also known as R1699W, is a SNP in the BRCA1 gene. The more common (C) allele encodes the amino acid arginine (R), while the rare (T) allele encodes a tryptophan (W).
An analysis of sequence variants of unknown clinical significance in the BRCA1 and BRCA2 genes concluded that this SNP was among the top 10 (over both genes) likely to lead to breast cancer, with a calculated odds of over 1,000:1 against this just being a spurious association. Although the clinical importance has not been proven, this may still be of use for genetic counseling.[PMID 17924331]

This SNP is also represented on some 23andMe microarrays as i5010082.

https://www.snpedia.com/index.php/Rs55770810

Categories: Is a snp | In dbSNP | SNPs on chromosome 17 | Has genotype | On chip 23andMe v3 | On chip 23andMe v4 | On chip Ancestry v2

Orientation	minus
Stabilized	minus

Geno	Mag	Summary
(C;C)	0	normal
(C;T)	5	carrier of BRCA1 variant likely to be pathogenic
(T;T)	5	carrier of two copies of BRCA1 variant; likely to be at higher risk for breast/ovarian cancer

Reference	GRCh38 38.1/141
Chromosome	17
Position	43063931
Gene	BRCA1
is a	snp

In the BRCA1 gene – which is 193,689 nucleotides long – if this 1 particular nucleotide is a T instead of a C, a person is more likely to get breast cancer.

BRCA1 SNPs – "You have the breast cancer gene."

- Approximately 500 of the 1,600+ known BRCA1 variants have been classified as **causal**.
- What should a person with a **BRCA1 variant that is causal** expect?
  - Increased risk of developing breast and/or ovarian cancer at an earlier age
  - Lifetime risk of breast cancer is 80 to 90%
  - Lifetime risk of ovarian cancer is 40 to 50%
  - Increased risk of bilateral breast cancer

Credit: OMIM
http://www.omim.org/clinicalSynopsis/604370

Credit SNPedia
https://www.snpedia.com/index.php/BRCA1

Variants of Unknown Significance (VUSs)

Yes! A variant (SNP) is present in a gene. (We don't typically see that nucleotide in that location.)

No! We don't know what the clinical significance is. It could be benign, or it could be pathogenic.

A VUS in a lab report really is UNKNOWN.

After more evidence is collected, VUSs can often be categorized as benign or pathogenic.

Clinicians Are Concerned with Clinically Actionable Variants

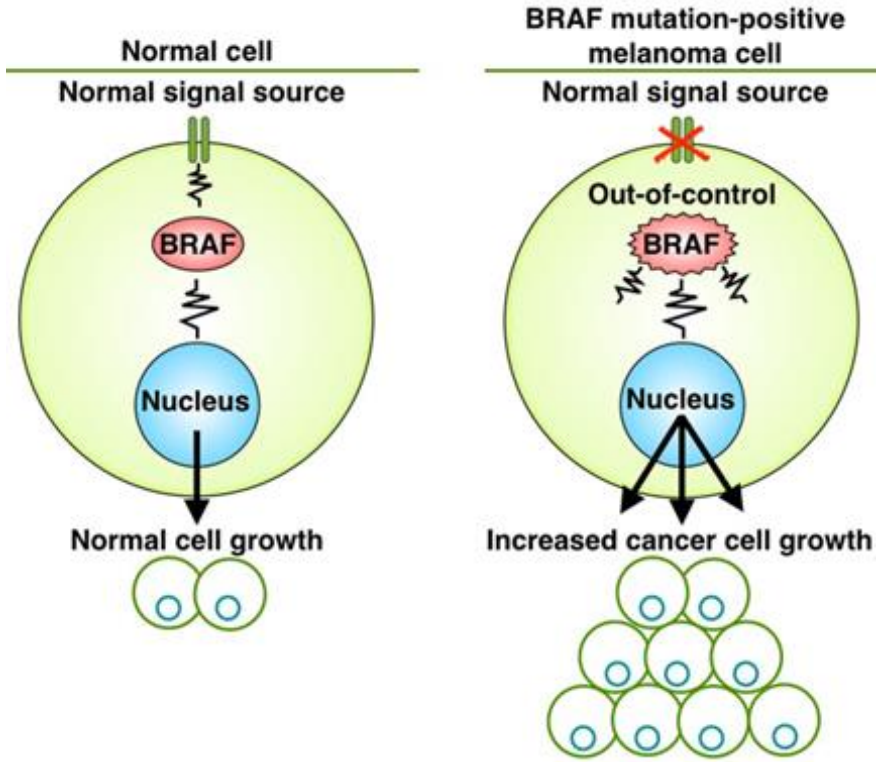
- If you have a BRCA1 pathogenic variant, clinician may be able to provide:
  - Closer surveillance (MRI in addition to mammogram)
  - Surgery (if warranted)
  - Chemoprevention
  - Genetic Counseling

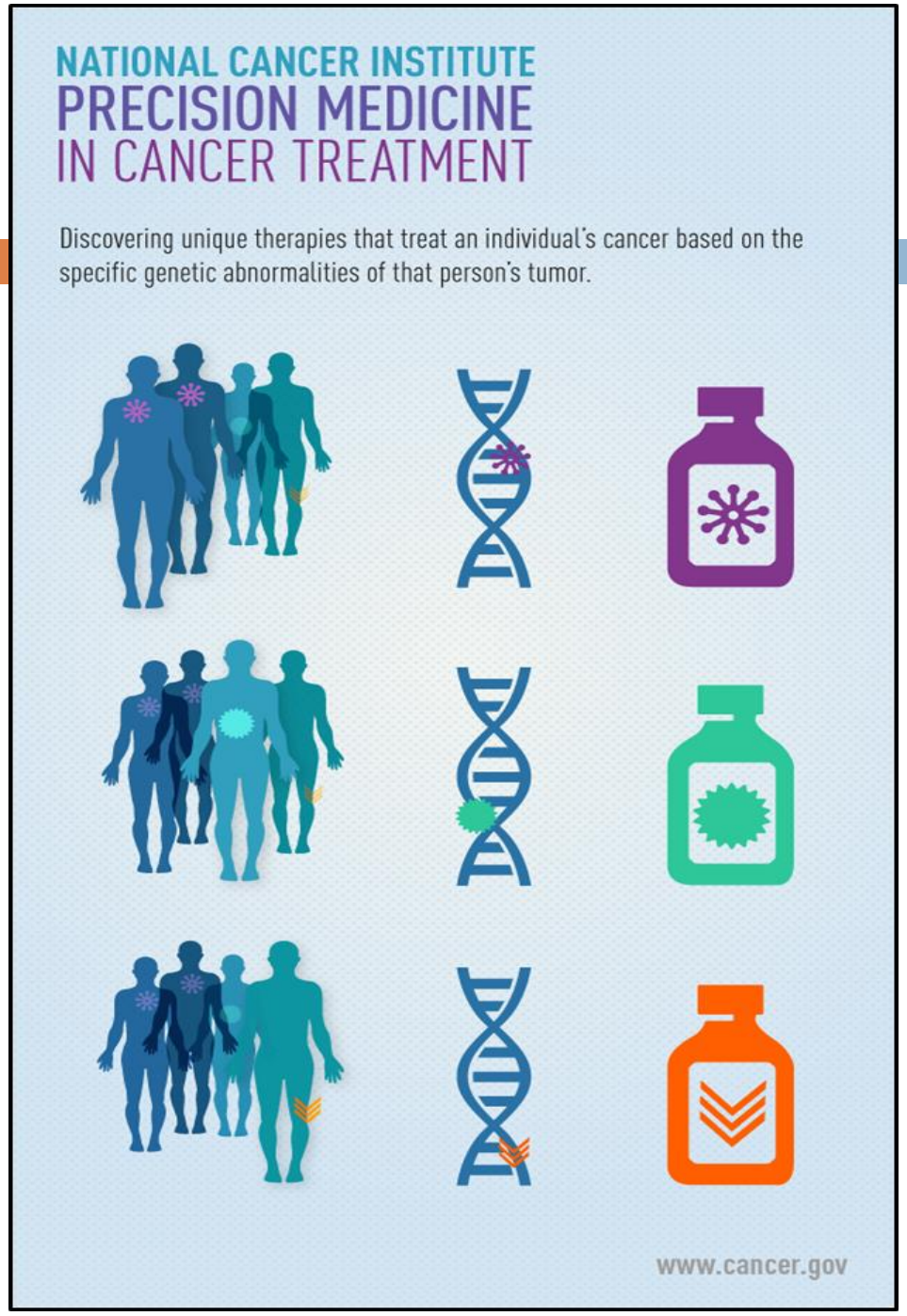
- Often the significance of a gene variant isn't known, or there isn't a helpful clinical way to address a gene variant.

3. Tumor Genomic Testing For Targeted Therapy

1. Researchers study genetic differences between tumor cells and normal cells.
2. Some tumor cells divide rapidly because their BRAF gene is not functioning properly.
3. Drugs are developed to target cells with this particular BRAF mutation.

Melanoma Cell With a BRAF V600 Mutation





PRECISION MEDICINE

Image credit Cancer.gov: http://www.cancer.gov/research/key-initiatives/precision-medicine

If Your Tumor Cells Have This Mutation, Then We'll Prescribe This Drug

Some Drugs Are Approved Along With "Companion Diagnostic Tests"

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAFINLAR safely and effectively. See full prescribing information for TAFINLAR.

TAFINLAR® (dabrafenib) capsules, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	11/2015
Dosage and Administration (2)	11/2015
Warnings and Precautions (5)	11/2015

----------INDICATIONS AND USAGE----------

- TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1, 2.1, 14.1)
- TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2, 2.1, 14.2)

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma. (1.3, 5.2)

----------DOSAGE AND ADMINISTRATION----------

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. (2.1)
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. (2.1)

Precision Medicine in Oncology

Table 1. Drug Targets and Their FDA-Approved Companion Diagnostic Tests

Drug	Target[a]	Indication[a]	Diagnostic Tests[a]
Trastuzumab	HER2/Neu Amplification[b]	Breast Cancer	Bond Oracle Her2 IHC System
			INFORM HER2 DUAL ISH DNA Probe Cocktail
			INSITE HER-2/NEU KIT
			SPOT-LIGHT HER2 CISH Kit
			PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody
		Localized, lymph node-negative breast cancer	INFORM HER-2/NEU
		Stage II, lymph node-positive breast cancer	HER2 CISH PharmDx Kit
			PATHVYSION HER-2 DNA Probe Kit
Trastuzumab/Pertuzumab/ Ado-Trastuzumab Emtansine		Breast cancer & gastric cancer	HER2 FISH PharmDx Kit
			HERCEPTEST
Crizotinib	ALK rearrangement	NSCLC	VENTANA ALK (D5F3) CDx Assay
			VYSIS ALK Break Apart FISH Probe Kit
Afatinib	EGFR Exon 19 deletion or L858R	NSCLC	*therascreen* EGFR RGQ PCR Kit
Erlotinib			cobas EGFR Mutation Test
Gefitinib			*therascreen* EGFR RGQ PCR Kit
Osimertinib	EGFR T790M	NSCLC	cobas EGFR Mutation Test v2[c]
Cetuximab/Panitumumab	EGFR Expression	CRC	DAKO EGFR PharmDx Kit
	KRAS Codon 12/13		cobas KRAS Mutation Test
			therascreen KRAS RGQ PCR Kit
Dabrafenib/Trametinib	BRAF V600E	Melanoma	THxID BRAF Kit[d]
Vemurafenib			cobas 4800 BRAF V600 Mutation Test
Pembrolizumab	PD-L1 Expression	NSCLC	PD-L1 IHC 22C3 PharmDx
Imatinib Mesylate	c-Kit	GIST	DAKO C-kit PharmDx
	KIT D816V	ASM	KIT D816V Mutation Detection by PCR
	PDGFRB	MDS/MPD	PDGFRB FISH
Olaparib	Germline BRCA1/BRCA2	Ovarian cancer	BRACAnalysis CDx
Venetoclax	17p deletion	CLL	VYSIS CLL FISH Probe Kit

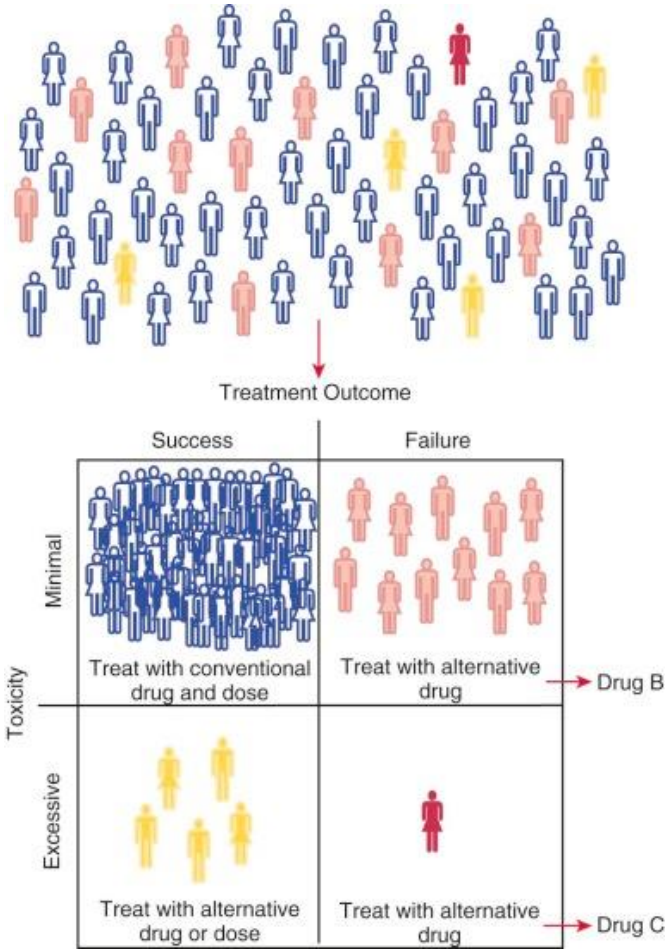
Schmidt KT et al. Precision Oncology Medicine: The Clinical Relevance of Patient Specific Biomarkers Used to Optimize Cancer Treatment. J Clin Pharmacol. 2016 May 16. PMID: 27197880.

4. Pharmacogenomics: Should We Prescribe You a Little, a Lot, or None At All?

Pharmacogenomics

Purpose: Study how genes affect an individual's responses to drugs.

Goal: Predict who will benefit from a medication, who will not respond at all, and who will experience adverse drug reactions.



(Adapted from Yaffe SJ, Aranda JV: *Neonatal and pediatric pharmacology* , ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)

Plavix (Clopidogrel)

- Anti-platelet drug – inhibits blood clots which can lead to heart attack and stroke.
- Some people have CYP2C19 variants that cause them to metabolize Plavix slowly.
- Slow metabolism of Plavix = increased risk of clotting/adverse events.
- Physicians will prescribe different antiplatelet drugs for these people.

BOXED WARNING (WHAT IS THIS?)

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)] ...

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see WARNINGS AND PRECAUTIONS (5.1)]*. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see CLINICAL PHARMACOLOGY (12.5)]*. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers *[see DOSAGE AND ADMINISTRATION (2.3)]*.

FDA-Approved Drugs with Pharmacogenomic Information in Their Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

165 drugs on this FDA list as of October 2016.

Sometimes genetic testing is mandatory for prescribing a drug.

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Pharmacogenomic information can appear in different sections of the labeling depending on the actions. For more information, please refer to the appropriate labeling guidance.

Therapeutic areas include anesthesiology, cardiology, dermatology, endocrinology, gastroenterology, hematology, infectious diseases, and psychiatry. The largest number are oncology drugs.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

Barriers to Use of Pharmacogenomic Testing in Clinical Practice

Table 2: Practical issues involved in clinical implementation of pharmacogenomic testing in healthcare system.

Issue	Challenge
Test performance	Reasonable turnaround time for delivery of test result
Interpretation of result	Not a straightforward normal versus abnormal interpretation Education of clinicians is crucial to proper use
Education of health professionals	Variable time and content devoted to educating future clinicians within health professional schools Overwhelming information for most current practicing clinicians
Cost reimbursement by payers	Almost exclusively based on proof of cost-effectiveness
Acceptance by clinicians	Potential additional workload Potential legal liability Health disparity concern for patient
Acceptance by patients	Privacy and discrimination concern Health disparity concern Ownership of genetic information

Y. W. Francis Lam, "Scientific Challenges and Implementation Barriers to Translation of Pharmacogenomics in Clinical Practice," ISRN Pharmacology, vol. 2013, Article ID 641089, 2013.

Survey of >10,000 US physicians: "Although 98% of all respondents agreed that the genetic profile of a patient could influence drug therapy decision, only 29% had received some pharmacogenomics education during their medical training, and **only 10% felt they were adequately trained to apply the knowledge in clinical practice."**

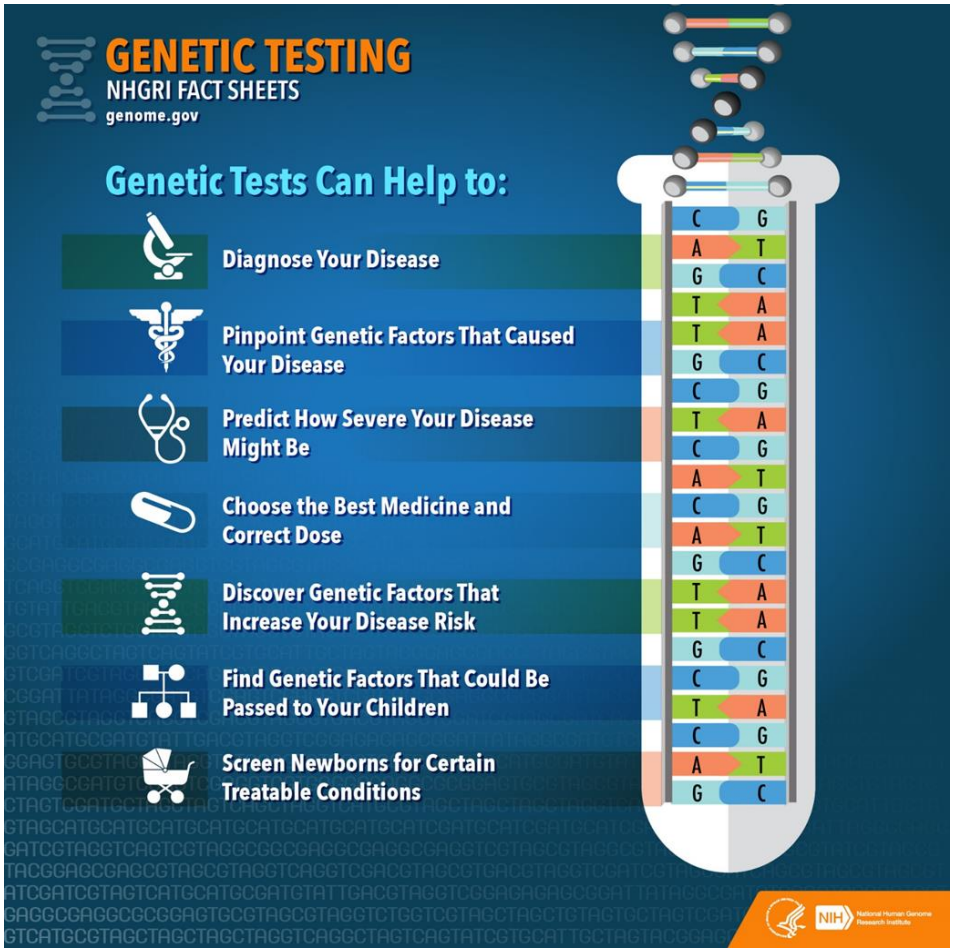
E. J. Stanek, C. L. Sanders, K. A. Taber et al., "Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey," Clinical Pharmacology and Therapeutics, vol. 91, pp. 450–458, 2012.

1000 Genomes Project

Credit Flickr - https://www.flickr.com/photos/trevor-dennis/

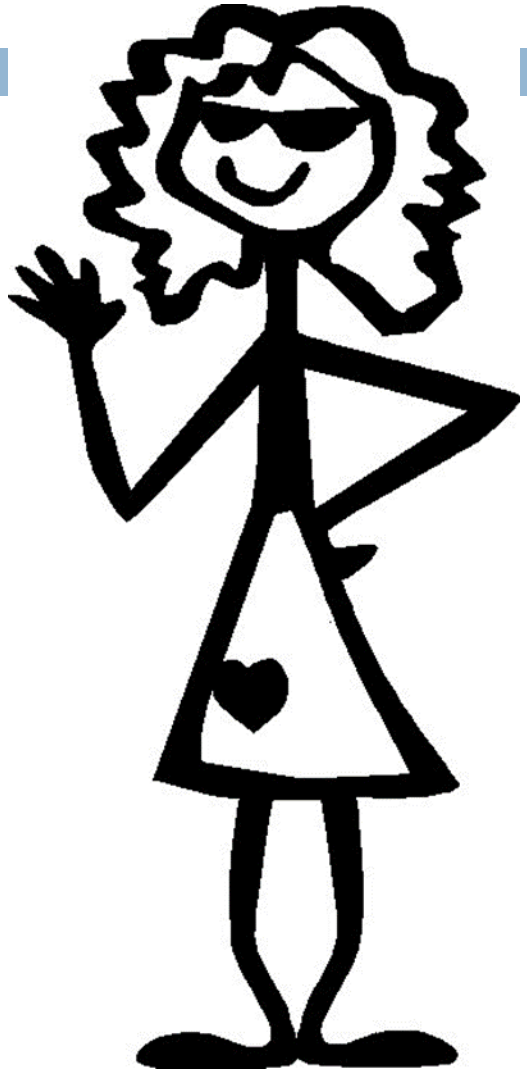
- Conducted to permit the study of genetic variation in the human population. (Completed 2015.)
- Analyzed 2,504 genomes from 26 populations across 5 continental regions.
- Increased diversity in genetic databases still needed!

Clinical Uses of Genetic Tests



Genetic Testing image from Genome.gov - https://www.genome.gov/images/content/genetic_testing.jpg

Jean's Genetic Testing Timeline



Age 1 Day: **newborn testing** for a few serious childhood diseases

Age 30: **carrier testing** (with her partner) before getting pregnant

Age 35: **predictive testing** when sister develops breast cancer at a young age

Age 45: **direct-to-consumer testing** to investigate ancestry

Age 65: **pharmacogenomics testing** when Plavix (anti-platelet drug) was not effective

Repeat Testing May Yield Different Results!

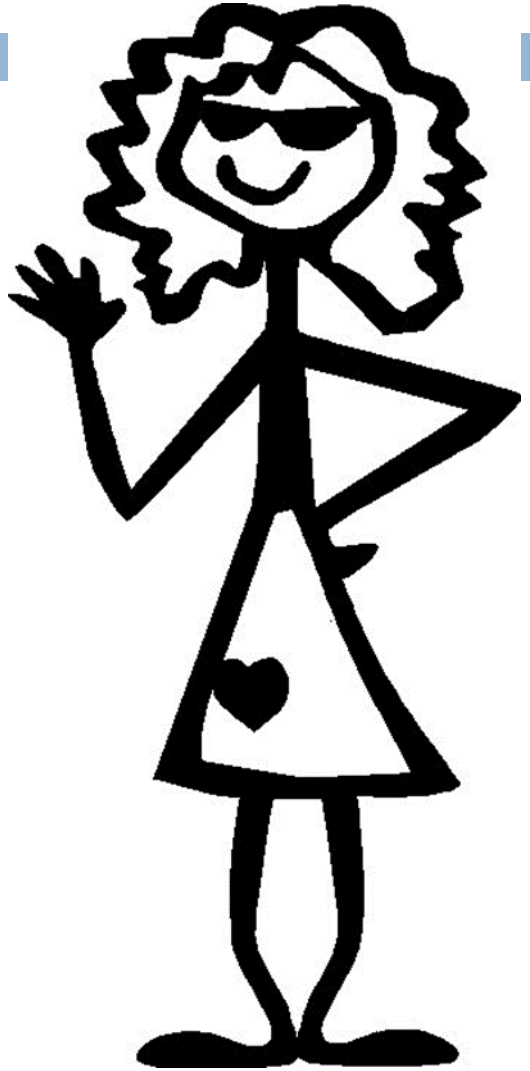
What genes and what variants did you test for?

- Different tests offered for the same conditions.
- Knowledge always changing.

Might not have enough examples in the database to determine associations between specific variants and specific conditions.

Might not have enough examples of people like you in the database.

Possibility of false positive and false negative results.

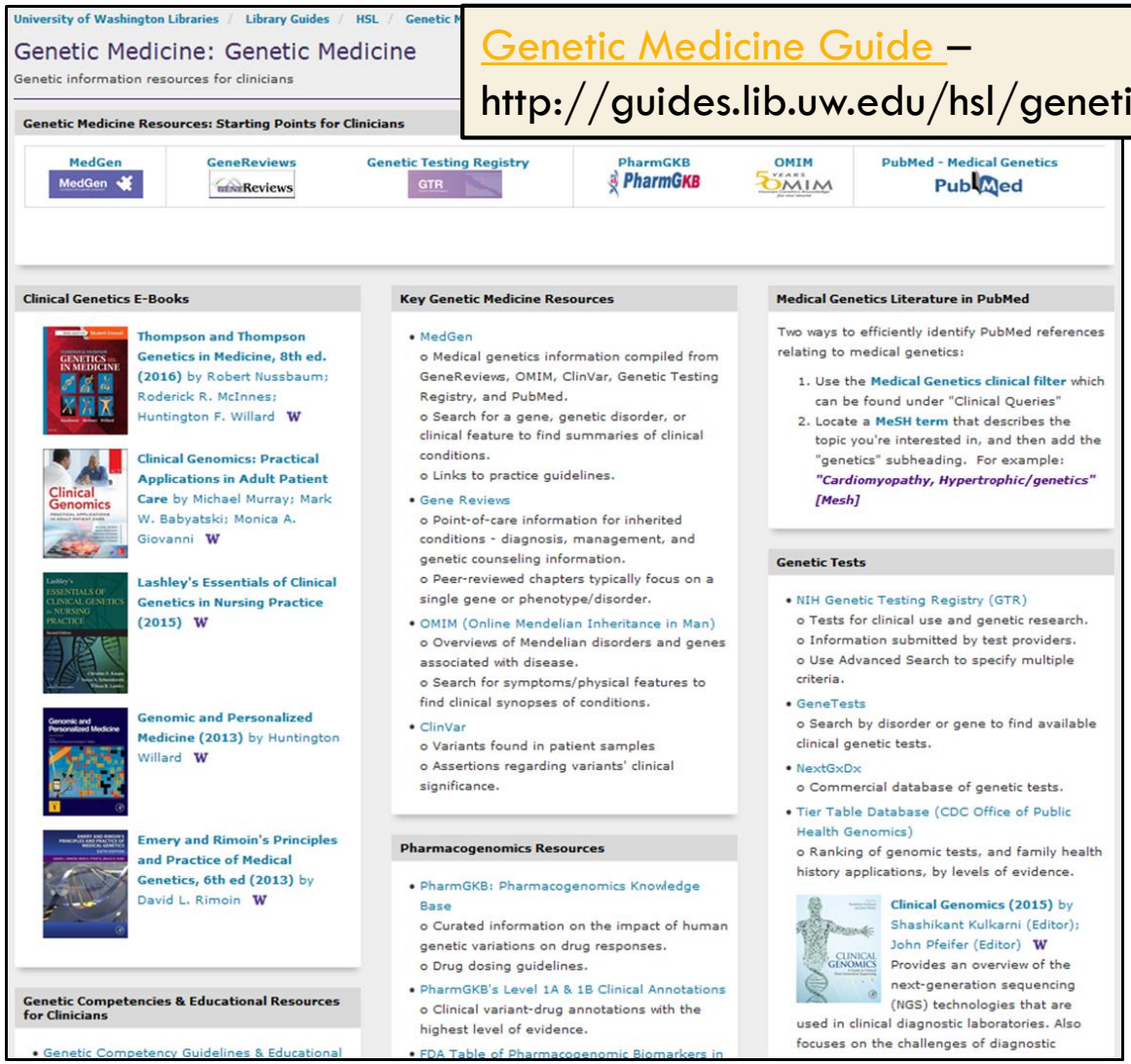


TAKE A BREAK!

Selected Genetic Medicine Databases for Clinicians

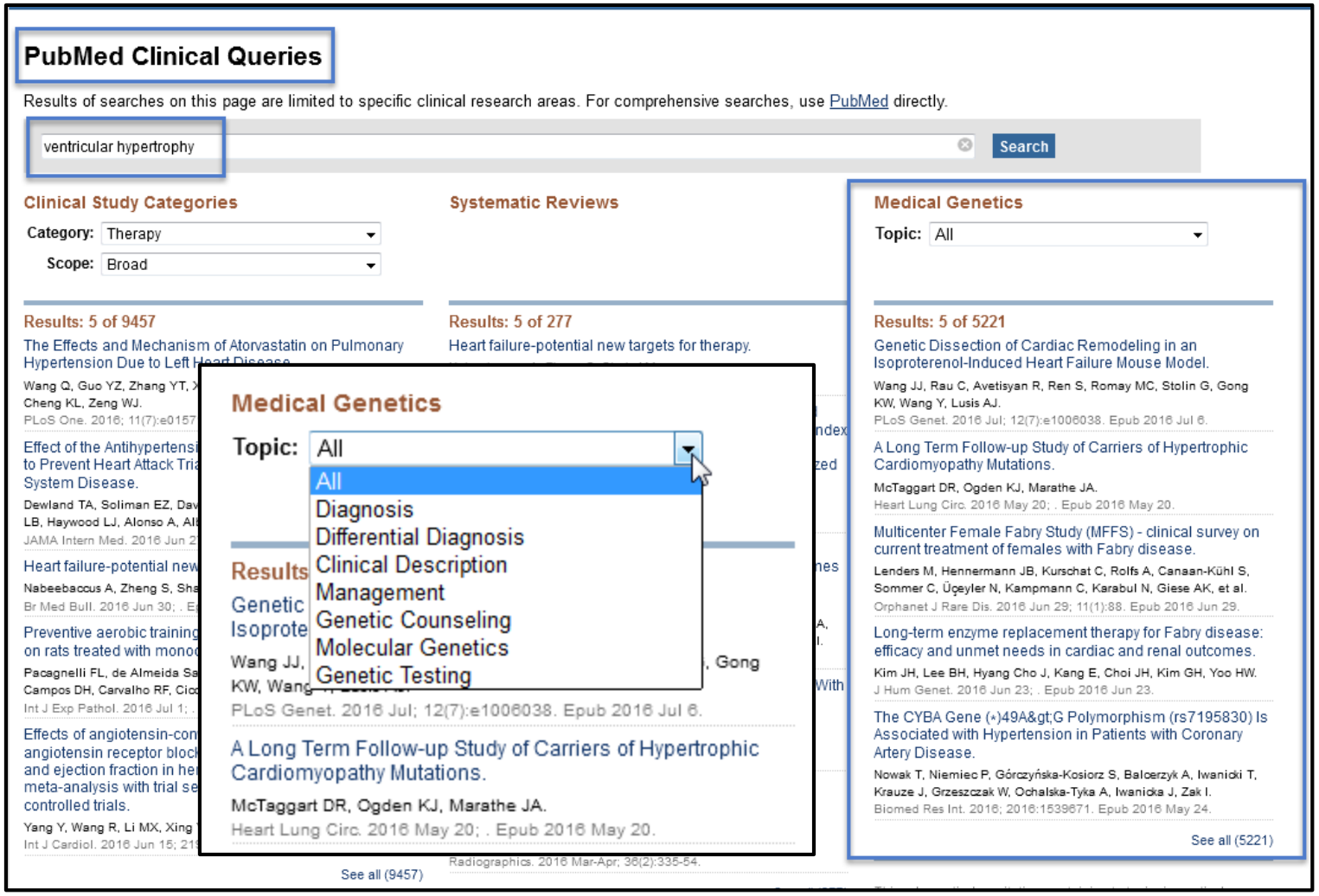
MedGen portal	Medical genetics information compiled from GeneReviews, OMIM, ClinVar, Genetic Testing Registry, practice guidelines, and PubMed. Links to consumer information.
Gene Reviews	Point-of-care information for inherited conditions - diagnosis, management, and genetic counseling information. Peer-reviewed chapters. Search by gene or disorder.
OMIM	Overviews of Mendelian disorders and genes associated with disease. Can search by symptom.
GTR: Genetic Testing Registry	Tests for clinical use and genetic research. Individual genes and gene panels. Information submitted by test providers.
ClinVar	Variants found in patient samples along with assertions regarding the variants' clinical significance. Includes level of evidence available.
PharmGKB	Information on the impact of human genetic variations on drug response. Includes drug dosing guidelines.

UW Genetic Medicine Guide

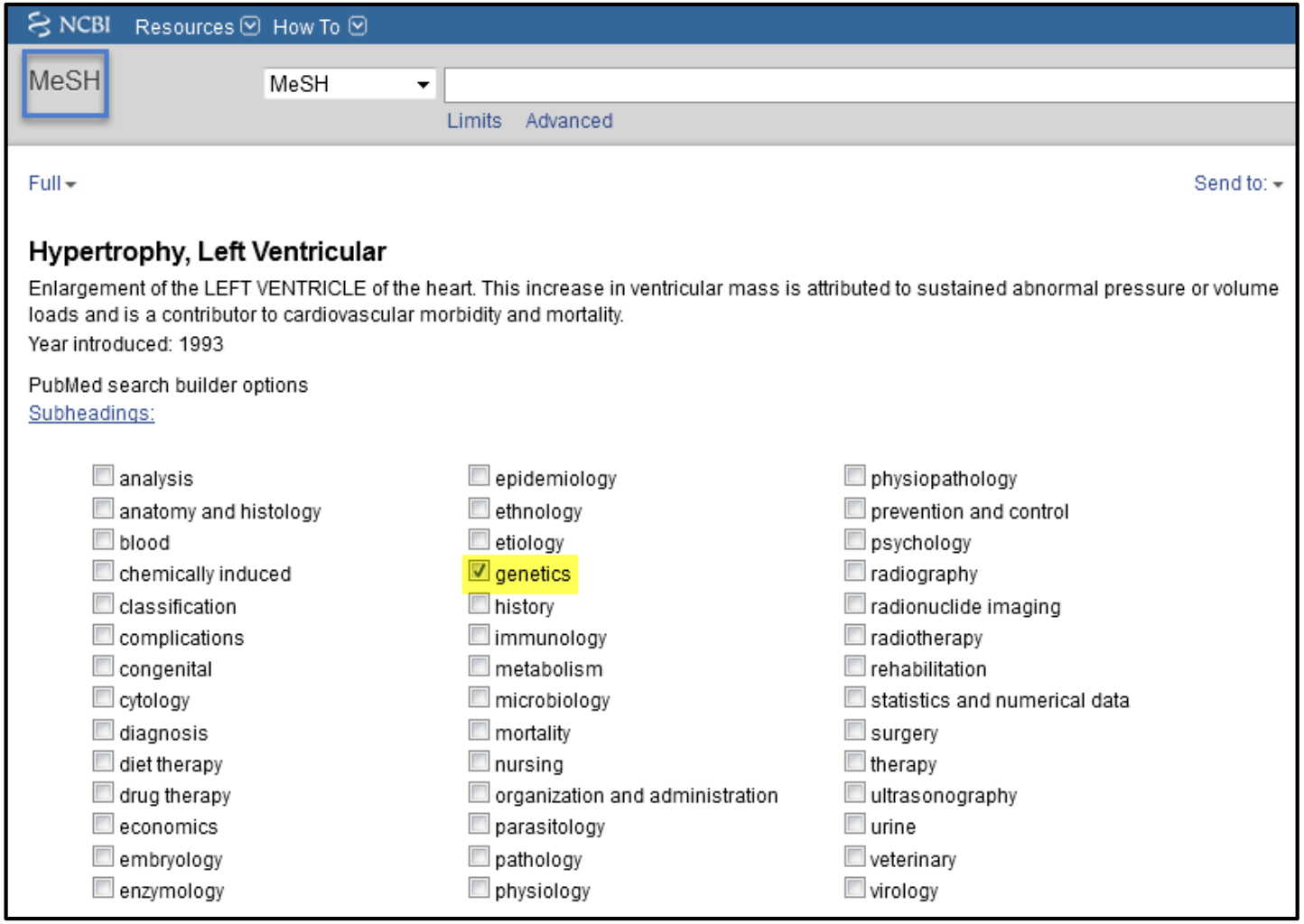


Genetic Medicine Guide – http://guides.lib.uw.edu/hsl/geneticmedicine

PubMed Medical Genetics Query

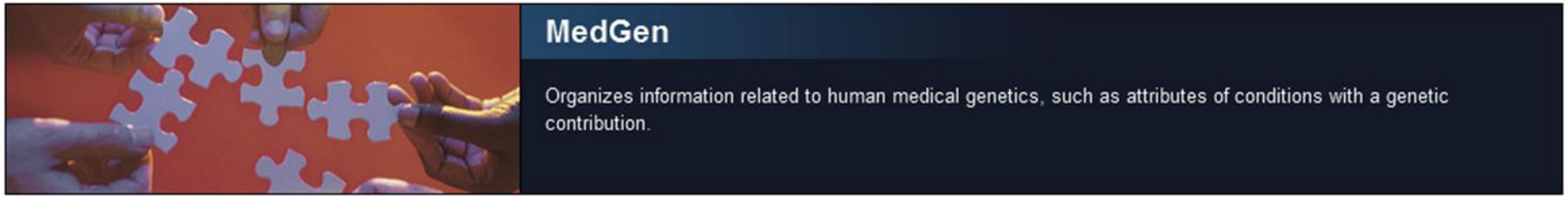


Genetics Subheading



NCBI's MedGen Portal

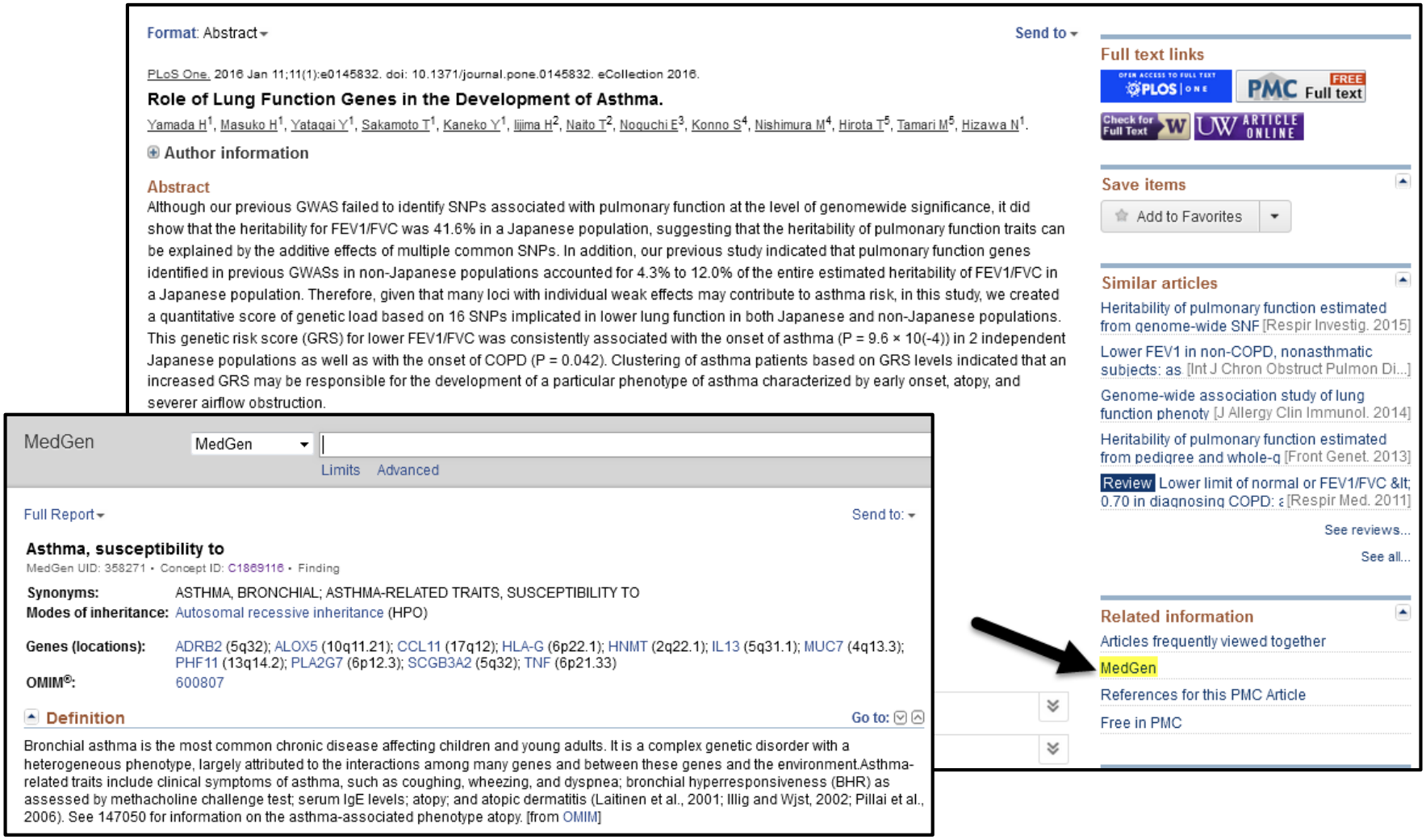
http://www.ncbi.nlm.nih.gov/medgen



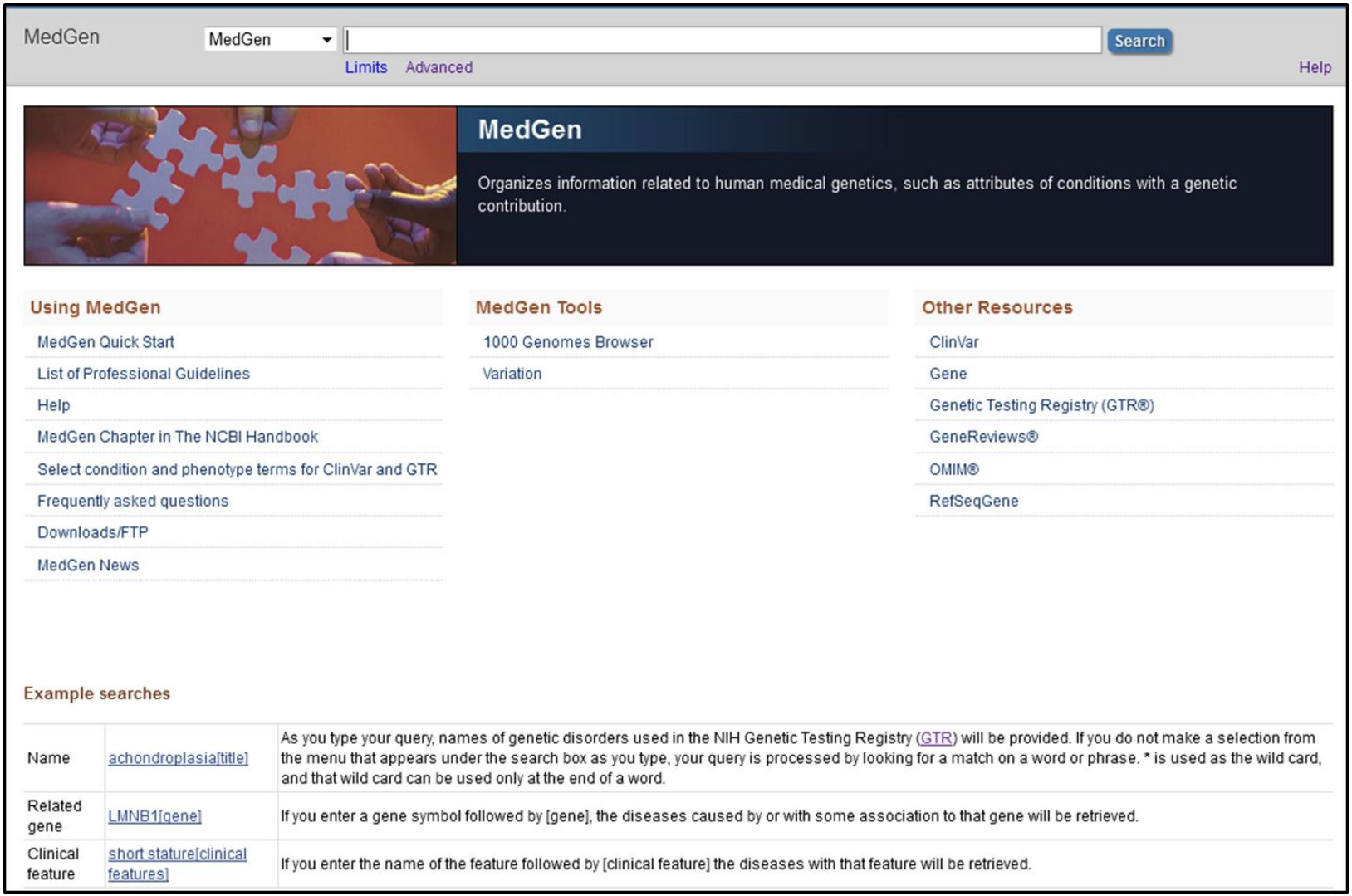
MedGen: NCBI Portal to Medical Genetics Content

- New and evolving NCBI resource. Development began in 2012.
- Information about human disorders and features or symptoms that have a genetic component.
- Designed for health care professionals and the medical genetics community.
- Compiles information from multiple sources: GeneReviews, OMIM, Genetic Testing Registry, ClinVar, Genetics Home Reference, practice guidelines, and PubMed.

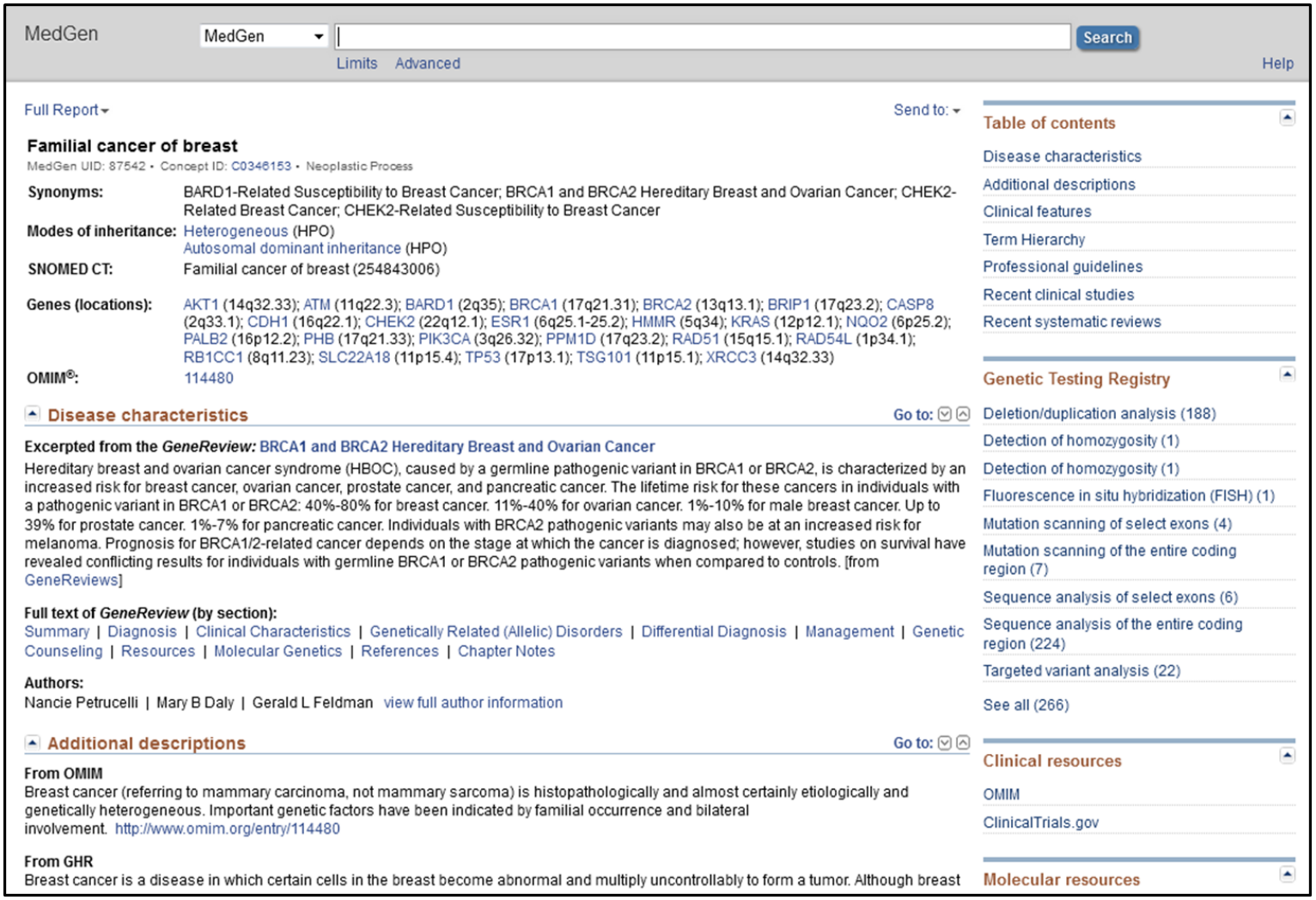
Good Search Strategy Is Following a Link from a PubMed Reference to MedGen



Exploration of MedGen Together



MedGen Summary – Familial Cancer of Breast



MedGen | MedGen | Search | Limits | Advanced | Help

Full Report | Send to:

Familial cancer of breast

MedGen UID: 87542 • Concept ID: C0346153 • Neoplastic Process

Synonyms: BARD1-Related Susceptibility to Breast Cancer; BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer; CHEK2-Related Breast Cancer; CHEK2-Related Susceptibility to Breast Cancer

Modes of inheritance: Heterogeneous (HPO)
Autosomal dominant inheritance (HPO)

SNOMED CT: Familial cancer of breast (254843006)

Genes (locations): AKT1 (14q32.33); ATM (11q22.3); BARD1 (2q35); BRCA1 (17q21.31); BRCA2 (13q13.1); BRIP1 (17q23.2); CASP8 (2q33.1); CDH1 (16q22.1); CHEK2 (22q12.1); ESR1 (6q25.1-25.2); HMMR (5q34); KRAS (12p12.1); NQO2 (6p25.2); PALB2 (16p12.2); PHB (17q21.33); PIK3CA (3q26.32); PPM1D (17q23.2); RAD51 (15q15.1); RAD54L (1p34.1); RB1CC1 (8q11.23); SLC22A18 (11p15.4); TP53 (17p13.1); TSG101 (11p15.1); XRCC3 (14q32.33)

OMIM®: 114480

Disease characteristics

Go to:

Excerpted from the *GeneReview:* BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer

Hereditary breast and ovarian cancer syndrome (HBOC), caused by a germline pathogenic variant in BRCA1 or BRCA2, is characterized by an increased risk for breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer. The lifetime risk for these cancers in individuals with a pathogenic variant in BRCA1 or BRCA2: 40%-80% for breast cancer. 11%-40% for ovarian cancer. 1%-10% for male breast cancer. Up to 39% for prostate cancer. 1%-7% for pancreatic cancer. Individuals with BRCA2 pathogenic variants may also be at an increased risk for melanoma. Prognosis for BRCA1/2-related cancer depends on the stage at which the cancer is diagnosed; however, studies on survival have revealed conflicting results for individuals with germline BRCA1 or BRCA2 pathogenic variants when compared to controls. [from GeneReviews]

Full text of *GeneReview* (by section):
Summary | Diagnosis | Clinical Characteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | References | Chapter Notes

Authors:
Nancie Petrucelli | Mary B Daly | Gerald L Feldman view full author information

Additional descriptions

Go to:

From OMIM
Breast cancer (referring to mammary carcinoma, not mammary sarcoma) is histopathologically and almost certainly etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement. http://www.omim.org/entry/114480

From GHR
Breast cancer is a disease in which certain cells in the breast become abnormal and multiply uncontrollably to form a tumor. Although breast

Table of contents

- Disease characteristics
- Additional descriptions
- Clinical features
- Term Hierarchy
- Professional guidelines
- Recent clinical studies
- Recent systematic reviews

Genetic Testing Registry

- Deletion/duplication analysis (188)
- Detection of homozygosity (1)
- Detection of homozygosity (1)
- Fluorescence in situ hybridization (FISH) (1)
- Mutation scanning of select exons (4)
- Mutation scanning of the entire coding region (7)
- Sequence analysis of select exons (6)
- Sequence analysis of the entire coding region (224)
- Targeted variant analysis (22)

See all (266)

Clinical resources

- OMIM
- ClinicalTrials.gov

Molecular resources

Practice Question #1 Using MedGen

Find a data-rich record for Alzheimer Disease. Make a note of the MedGen UID.

- What genes are associated with Alzheimer Disease?
- According to Gene Reviews, what are the causes of Alzheimer Disease?
- Are there practice guidelines for primary care providers on diagnosing Alzheimer Disease? What year were they written?
- BONUS: Does the Genetic Testing Registry include panels of genes for diagnosing Alzheimer Disease?

Practice Question #2 Using MedGen

A physician suspects that her patient doesn't respond well to clopidogrel.

- Find a MedGen record that addresses this phenomenon.
- What gene is involved in metabolizing clopidogrel?
- When were the most recent practice guidelines for clopidogrel dosing published ?
- What percentage of Chinese people are thought to be poor metabolizers of clopidogrel? *[Hint: Medical Genetics summaries link]*
- Can you find some information that may be helpful for the patient?
- BONUS: What database has detailed information on the effects of gene variants on drug response? *[Hint: It's linked from MedGen record.]*

TAKE A BREAK!

Show What You Know!

- The 1000 Genomes Project was undertaken in order to increase the _____ of the genomes represented in public databases.
- What term refers to strategies for determining what treatment is right for an INDIVIDUAL rather than what treatment is recommended for a DISEASE?
- Clinicians are not concerned about <u>all</u> genetic variants – only those that are _____.
- True or False? GINA (Genetic Information Nondiscrimination Act) protects you from life insurance discrimination.
- True or False? A genetic variant may originally be classified as "likely pathogenic" and later classified as "likely benign."
- What resource would you recommend to consumers who wanted to learn more about a genetic condition?
- What is a good starting place for finding genetic information for clinicians?